Support for new Claims 21 and 22 may be found on page 7, lines 2-7, page 8, lines 26-28, and on page 14, line 24 through page 15, line 5.

Support for new Claim 23 is provided by Claim 1 as originally filed, and, for example, in the specification on page 6, lines 16-20.

Support for new Claim 24 may be found on page 7, lines 2-7, page 8, lines 26-28, and on page 14, line 24 through page 15, line 5.

Support for new Claim 25 may be found on page 15, line 26 through page 16, line 8.

Enablement of the Amended Claims

The claims are all directed to combinations of a gastrin/CCK receptor ligand and an epidermal growth factor receptor ligand administered *in vivo* or *ex vivo*, and include claims for effecting differentiation of pancreatic islet precursor cells to mature insulin-secreting cells (Claims 1-3, 19 and 23), inducing proliferation of mature insulin-secreting β-cells (Claims 4-7, 20-22, 24), and a kit comprising pancreatic islet precursor cells treated *ex vivo* with a gastrin/CCK receptor ligand and an EGF receptor ligand (Claim 25). The use of the particular language of a gastrin/CCK receptor ligand and an epidermal growth factor receptor ligand is enabled by the specification, and the knowledge in the art that gastrin, TGF-α, related proteinaceous compounds, and proteins with similar functions can act in equivalent fashion on a variety of epidermal and gastrointestinal cells.

It is well known in the art that gastrin/CCK receptor ligands are able to stimulate the gastrin/CCK receptors of pancreatic cells. For example, Sallian-Barreau *et al.* postulate that gastrin is expressed during development of the pancreas and is believed to act on islet cell differentiation and growth (*Diabetes* 1999 Oct. **48**: 2015-2021). After the priority date of the present application, Rooman *et al.* demonstrate that gastrin, teragastrin (cholecystokinin fragment 30-33), pentagastrin, rat gastrin I and rat gastrin II induce proliferation *in vitro* and *in vivo*, and differentiation *in vitro*, of duct-like pancreatic epithelial cells that express gastrin/CCK-B receptors (2000, Sept., *36th Ann Congress European Assoc Study Diabetes*; and *Gastroenterol* 2001, Oct. **121:4** 940-949). Baldwin shows that both gastrin and cholecystokinin act as

proliferation factors for pancreatic cells *in vivo*, and cholecystokinin in particular enhances induction of acinar tumors by carcinogens (*J Gastroenterol Hepatol* 1995, Mar-Apr. **10:2** 215-232).

It is also known in the art that EGF receptor ligands are able to induce proliferative responses in gastrointestinal tissues. For example, Goodlad, *et al.*, (*Clin Sci* 1996, Oct **91**: 503-507) teaches that both EGF1-53 and EGF1-48 act as mitogens for epithelial cells (hepatocytes) *in vivo* and *in vitro*. Guglietta *et al.*, and Amarant *et al.* teach that, because or their mitogenic properties, EGF1-48 and its EGF1-47 and hEGF1-49 congeners may be used to treat gastrointestinal lesions (WO9202246 and WO9314783). Reindel *et al.*, (*Toxicol Pathol* 1996, 24: 669-680) show that EGF1-48 is able to induce cellular proliferation in pancreatic ducts.

Nardi *et al.* (USPN 5,885,956, and USPN 6,288,301) demonstrate that a gastrin/CCK receptor ligand combined with a EGF receptor ligand are able to increase pancreatic islet mass, stimulate pancreatic islet cell neogenesis, and effect the differentiation of pancreatic islet precursor cells *in vivo*. Examples of gastrin/CCK receptors included gastrin such as gastrin 34, gastrin 17, and gastrin 8, various forms of cholecystokinin such as CCK 58, CCK 33, CCK 22, CCK 12 and CCK 8; and other gastrin/CCK receptor ligands with the same synergistic activity with EGF receptor ligands and have a carboxy terminal peptide Trp-Met-Asp-Phe-amide. Nardi *et al.* also show that EGF receptor ligands such as EGF1-53, including EGF1-48, EGF1-52, EGF1-49 and fragments and active analogs thereof, TGFα receptor ligands (1-50) including 1-48, 1-47 and amphiregulin and pox virus growth factor and active analogs, fragments and modifications of the above may induce neogenesis of insulin-producing pancreatic islet cells. In summary, the breadth of the claims are enabled both by the present specification, which discloses numerous gastrin/CCK receptor ligands and epidermal growth factor receptor ligands, and by the body of knowledge available to those skilled in the art, as evidenced by the above references, patents and publications which demonstrate a variety of ligands, including those claimed cause differentiation and/or proliferation of epidermal cells, including pancreatic cells.

Applicants believe no new matter has been introduced by these amendments and the Examiner is respectfully requested to enter the amendments. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 328-4400.

Respectfully submitted,

Dated: December 20, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Indu Parikh, *et al.*	)	Examiner: Not Yet Assigned
Serial No.: Not Yet Assigned	)	Art Unit: Not Yet Assigned
Filed: December 20, 2001	)	**VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE CLAIMS**
For: **TREATMENT FOR DIABETES**	)	

BOX Patent Application
Assistant Commissioner for Patents
PO Box 2327
Arlington, VA 22202

Sir:

These Marked-up Versions of the claims accompany the Preliminary Amendment for the above identified patent application.

IN THE CLAIMS

1. (Amended) A method for treating diabetes mellitus in an individual in need thereof, said method comprising:

administering to said individual a composition providing [at least one receptor ligand selected from the group consisting of] a gastrin/CCK receptor ligand and an EGF receptor ligand in an amount sufficient to effect differentiation of pancreatic islet precursor cells to mature insulin-secreting cells.

2. (Reiterated) The method according to Claim 1, wherein said at least one receptor

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Robert Pattison
(Signature)
Robert Pattison
(Printed Name)

its EGF1-47 congener of EGF1-48, and an EGF1-49 congener of EGF1-48.

3. (Reiterated) The method according to Claim 2, wherein said EGF1-53, EGF1-48, or its EGF1-47 or EGF1-49 congener is human EGF1-53, EGF1-48, or its EGF1-47 or EGF1-49 or its congener.

4. (Amended) A method for providing a patient with diabetes in need thereof with a population of mature insulin-secreting [beta] β-cells, said method comprising:

[transplanting into said patient cultured pancreatic islets which have been provided] providing pancreatic β-cells, outside said patient, with a sufficient amount of [at least one receptor selected from the group consisting of] a gastrin/CCK receptor ligand and an epidermal growth factor receptor ligand to induce proliferation of mature insulin-secreting [beta] β-cells of said [islets] pancreatic β-cells prior to said transplanting, whereby an expanded population of mature insulin-secreting β-cells is obtained; and

transplanting into said patient said mature insulin-secreting β-cells.

5. (Reiterated) The method according to Claim 4, wherein said diabetes is Type 2 diabetes.

6. (Reiterated) The method according to Claim 4, wherein said gastrin/CCK receptor ligand is a gastrin.

7. (Reiterated) The method according to Claim 4, wherein said epidermal growth receptor ligand is TGF-α or an EGF selected from the group consisting of EGF1-53, EGF1-48, or its EGF1-47 or EGF1-49 congener.

Cancel Claims 8-18 and add new claims 19-22.

--19. (New) The method according to Claim 1, wherein said gastrin/CCK receptor ligand is a gastrin.

20. (New) Pancreatic islet precursor cells treated *ex vivo* with a sufficient amount of a gastrin/CCK receptor ligand and an EGF receptor ligand to induce proliferation of said pancreatic islet precursor cells into mature insulin-secreting β-cells, whereby an expanded population of said mature insulin-secreting β-cells is obtained.

21. (New) A method for obtaining an expanded population of insulin-secreting pancreatic β-cells, said method comprising:

providing pancreatic islet precursor cells with a sufficient amount of a gastrin/CCK receptor ligand and an EGF receptor ligand to induce proliferation of said insulin secreting pancreatic β-cells, whereby said insulin-secreting population of pancreatic β-cells is obtained.

22. (New) The method according to Claim 21, wherein said providing is *ex vivo.*

23. (Amended) A method for treating diabetes mellitus in an individual in need thereof, said method comprising:

administering to said individual:

a composition providing a gastrin/CCK receptor ligand selected from the group consisting of gastrin and cholecystokinin; and

an EGF receptor ligand selected from the group consisting of EGF1-53, EGF1-48, or its EGF1-47 congener of EGF1-48, and an EGF1-49 congener of EGF1-48;

in an amount sufficient to effect differentiation of pancreatic islet precursor cells to mature insulin-secreting cells.

24. A method for obtaining an expanded population of insulin-secreting pancreatic β-cells *ex vivo*, said method comprising:

providing pancreatic islet precursor cells with a sufficient amount of;

a composition providing a gastrin/CCK receptor ligand selected from the group consisting of gastrin and cholecystokinin; and

a composition providing a gastrin/CCK receptor ligand selected from the group consisting of gastrin and cholecystokinin; and

an EGF receptor ligand selected from the group consisting of TGF-α, EGF1-53, EGF1-48, or its EGF1-47 congener of EGF1-48, and an EGF1-49 congener of EGF1-48;

whereby said insulin-secreting population of pancreatic β-cells is obtained.

25. A kit for use in the treatment of diabetes, comprising:

pancreatic islet precursor cells according to Claim 20.--

CONCLUSION

Should the Examiner have any questions regard the above, in order to expedite prosecution, the Examiner is invited to call the undersigned.

Respectfully submitted,

Dated: December 20, 2001

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